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Cytokines & Sepsis: BACKGROUND INFORMATION

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Cytokines & Sepsis

Sepsis, which often develops into life-threatening shock, is a systemic clinical situation caused by toxic substances released from microorganisms during severe infection. In humans, sepsis is commonly caused by endotoxins secreted from gram-negative bacteria. Septic chock is characterized by a drastic fall in blood pressure, cardiovascular collapse and multiple organ failure, and is responsible for over 100,000 dealths a year in the US alone. In the past 10 years, mortality in patients with sepsis has only slightly decreased, despite aggressive intensive care treatment. An entire medical specialty, called Critical Care Medicine, has developed around the septic patient, delivering hemodynamic, metabolic, ventilative and renal support. Yet, mortality of septic shock patients remains high at 35-45% even in the most sophisticated medical centers of the world.

Usually, the progression of sepsis into septic shock coincides with a rapid increase in circulating levels of inflammatory cytokines such as TNF-a, IFN-g, IL-1B, IL-8, and IL-6. The sudden increase in the concentration of these cytokines, also called a "cytokine storm", is believed to be the underlying reason for the onset of the shock. Support for the notion that cytokine "friendly fire" is a major factor responsible for the severity of sepsis and the likelihood of death, came from animal models showing that neutralizing antibodies to TNF-a, the first cytokine elaborated in the septic inflammatory cascade, prevented death in mice exposed to lethal injections of E. coli or endotoxin. Additional support came from studies showing that injections of either TNF-a or IL-1 mimic the physiological changes of septic shock, and that blocking IL-1 activity with IL-1 receptor antagonist (IL-1ra) was effective in protecting animals from lethal bacteremia or endotoxemia. These results strongly suggested that reducing the levels of circulating TNF-a and /or IL-1 can attenuate the progression of sepsis into septic shock and pointed toward the possibility that anti-cytokine therapy could be effective in reducing the risk of dying from spetic shock. Consequently, these anti-cytokine agents were taken into clinical trials.

Large groups of septic patients worldwide have been entered into these trials and treated with either IL-1ra

or anti-TNF-a. Ironically, despite the convincing pre-clinical data, the results with either agent showed only a small reduction in mortality, in the range of 3-4%. However, it remains unclear wheither the agents themselves were ineffective or whether the trials were inadequate to show a significant therapeutic benefit. Further analysis of the data which emerged from 18 clinical trials suggested that the survival benefit associated with anti-cytokine therapy can be as high as 15% for some sub-groups of patients. Improvement in treating **septic** patients, using anti-cytokine regimes,can be achieved primarily by initiating early treatment. Additional gains can be achieved through selection of patients who stand a higher chance to benefit from the treatment. That the timing of initiation of treatment for sepsis is crucial to successful treatment has been clearly demonstrated in animal models.

For example, in baboon studies, when treatment was instituted within two hours of sepsis induction, all survived, but when treatment was delayed for four hours, death occured. A clinical trial using anti-TNF therapy demonstrated the importance of identifying patients who would best respond to the anti-cytokine treatment. In that trial, it was found that the reduction in mortality, employing anti-TNF Fab'2 antibodies, was observed primarily in patients who had high levels, greater than 1ng/ml, of circulating IL-6 upon entry into the study. On the other hand, patients who had low levels of IL-6 did not benefit from the anti-TNF treatment. In that study, a single measurement of serum IL-6 was sufficient to distinguish between two sub-groups. Based on these results, a second trial in which the criteria of elevated IL-6 levels will be used in the analysis of the data is presently ongoing.

It is believed that rapid assays for cytokines should facilitate identification of **septic** patients undergoing a "cytokine storm" so that anti-cytokine therapy can be initiated early in the course of sepsis. In this setting, the maximal survival benefit from anti-cytokine therapy is expected. During endotoxemia, the sharp increase in the concentrations of proinflammatory cytokines is accompanied by elevated serum levels of nitric oxide(NO). Elevated serum levels of NO are thought to play a central roll in inducing cardiocascular dysfunction and tissue damage observed during **septic shock**. In fact, NO is believed to be the final common mediator in the inflammatory cascade leading to **septic shock**. In vitro studies have shown that the release of NO from most macrophage-like cells is upregulated by pro-in-flammatory cytokines such as IFN-g amd TNF-a, and down-regulated by anti-inflammatory cytokines such as IL-10 and IL-4.

Recently, the role of endogenous IFN-g,TNF-a and IL-10 in lipopolysaccharide (**LPS**) **induced** NO release was studied in a mouse model . Mice were pretreated with anti-IFN-g, anti-TNF-a andanti- IL-10 monoclonal antibodies, or a combination of these antibodies, or a combination of these antibodies, two hours prior to **LPS** challenge. The results indicated that blocking the anti-inflammatory effects of IL-10 with anti-IL-10 resulted in a two-fold increase in **LPS induced** serum NO as well as a seventeen-fold increase in the levels of IL-6, a thirty-fold increase in levels of TNF-a, and a five-fold increase in levels of IFN-g or TNF-a alone had no effect on **LPS induced** NO release. However, blocking both IFN-g and TNF-a almost completely prevented NO release after **LPS** challenge. These results clearly demonstrate that **LPS induced** NO release is mediated through at least two pathways, and further suggests that treating endotoxemia with both anti-IFN-g and anti-TNF-a would be much more efficient that treatment with either agent singly.

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